

DETAILED ACTION

Acknowledgement is made of the remarks/amendments filed 10/29/2009. Claims 46 and 49 were amended. Claims 1-36, 42-45 and 47-48 stand canceled. Claims 37-41, 46, and 49-62 are pending in the instant Office action.

Claim Rejections - 35 USC § 112 2nd Paragraph--Withdrawn

The rejection of claims 46 and 49 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the amendment to correct the dependency of these claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-41, 46, and 49-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. (US 6228401, as per Applicant's IDS).

The instant claims are drawn to a pharmaceutical formulation comprising crystalline and/or amorphous flutamide particles mixed with at least one surface-active substance wherein the size of 50% of the flutamide particles in the pharmaceutical formulation is greater than 26 μm (claim 37).

James et al. teach a pharmaceutical formulation comprising crystalline and/or amorphous flutamide particles mixed with at least one surface-active substance (Examples 6, 7, and 9). James does not explicitly state that the flutamide is crystalline and/or amorphous, however, because there are no other known forms that flutamide can be in, it must be crystalline and/or amorphous. The surface active substance is sodium lauryl sulfate which is an anionic compound as per claim 51. Sodium lauryl sulfate is the common name for sodium dodecylsulfate, as required by claim 52. James teaches that rotary cutters are one means of achieving the desired flutamide particle

size (col. 2, lines 37-38). Rotary cutters are a type of forced-action mixer; the blades are forced through the desired mixture. The instant specification at page 10, 3rd paragraph provides support for this statement. This paragraph states that "Conventional forced-action mixers with a stainless steel interior may be used for the process according to the invention. Forced-action mixers are generally mixers having a round or flat base and blades or paddles rotating close to the base. They may have so-called "choppers", that is, rapidly rotating knives, which project into the mixing vessel."

With respect to claims 38, 40 and 56, James teaches the formulation in the form of a tablet with at least one flow regulator (silica) in example 7. The tablet of example 7 could also be used as a suppository. The term suppository is an intended use and because the prior art structure is capable of performing the intended use, it meets the limitations of the claim, absent evidence to the contrary. With particular respect to claim 56, a tablet is considered a shaped article.

With respect to claim 39, James teaches the formulation as filling for capsules in examples 6 and 9.

With respect to claim 50, James teaches the flutamide is in the form of its free acid amide or a pharmaceutically acceptable salt thereof (col. 2, lines 4-5).

With respect to claims 53-55 which specify the weight ratio of flutamide to surface-active substance, James teaches a ratio of flutamide to surface-active substance of 10.4 to 1 which falls within, and thereby anticipates the ranges for claims 53-55 (Example 6).

With respect to claims 57-59 which specify the amount of flutamide in the formulation, James teaches 125 mg of flutamide in the formulation which falls within and thereby anticipates the amounts claimed (Example 6).

With respect to claim 60, all of the working examples of James comprise at least one excipient selected from inorganic fillers, organic fillers, binders, glidants, lubricants, flow regulators and disintegrants. See particularly Example 6 which further comprises lactose, povidone, corn starch, magnesium stearate and water in addition to flutamide and the surface-active substance sodium lauryl sulfate.

As discussed above, James et al. teach the exact same ingredients as required by the instant claims as well as the use of rotary cutters which is a type of forced-action mixer, which is the same process recited in the instant product-by-process claims. James et al. fails to explicitly teach wherein the size of 50% of the flutamide particles in the pharmaceutical formulation is greater than 26 microns as required in independent claim 37, or wherein 90% of the flutamide particles is greater than 130 microns as required by claim 46, or that the specific surface area less than $0.35 \text{ m}^2/\text{cm}^3$ as required by claim 49.

However, James et al. with respect to particle size and surface area teaches the following. James teaches specific examples wherein the X_{50} value of the flutamide particles is greater than $20 \text{ }\mu\text{m}$ (example 5, column 7, see example 3 from the table at lines 45-47, $X_{50} = 20.99 \text{ }\mu\text{m}$), and an example wherein the flutamide particles have a specific surface area of $0.47 \text{ m}^2/\text{cm}^3$ (example 5, column 7, see example 3 from the table at lines 45-47). James more generally teaches that the X_{50} for the particles is less

than 26.0 μ (col. 2, lines 23-24) and that typical X_{90} values for the particles is from about 10 to about 130.0 μ (col. 2, lines 28-29). With respect to claim 49 which specifies that the flutamide particles have specific surface area of 0.35 m^2/cm^3 , James teaches flutamide particles having a specific surface area of at least about 0.35 m^2/cm^3 . About 0.35 m^2/cm^3 overlaps with and thereby makes obvious the claimed value of less than 0.35 m^2/cm^3 . James et al. teach that means of achieving these particle sizes, distributions and surface areas include milling, but also the use of rotary cutters (i.e. forced-action mixer, see discussion above regarding page 10 of the instant specification), see col. 2, lines 37-38. Also, James teaches that particles of flutamide are known that range from 5 to 240 microns in size (col. 1, line 47). It is also well known in the art that that varying the mixing speed, the amount of flutamide fed into the mixer and the mixing period all influence the resulting size and surface area of the resultant flutamide particles. James also teaches that flutamide is relatively insoluble (col. 1, line 38) and that flutamide has a consistency which is difficult to mill due to the fact that it readily agglomerates and give inconsistent results (col. 2, lines 46-48). James teaches that the specific surface area of flutamide is critical for determining bioavailability of flutamide (col. 1, lines 52-54). James also teaches that the range of particle sizes contained in a sample of flutamide influences the bioavailability and thus the therapeutic benefit of the drug (col. 2, lines 17-20).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at particles with an X_{50} value greater than 26 microns and X_{90} values greater than 60 microns or 130 microns and particles with a

specific surface area of less than $0.35\text{m}^2/\text{cm}^3$ based on the teachings of James at the time of the instant invention with a reasonable expectation of success. One would have been motivated to do so because James teaches X_{50} and X_{90} values and specific surface areas that overlap with, or are very close to those ranges claimed by applicant. Furthermore, James teaches that flutamide is known to exist in particle sizes up to 240 microns and also teaches that it is known in the art to achieve similar particle sizes, as measured by X_{50} and X_{90} values, and different specific surface areas by using rotary cutters or other milling techniques. The rotary cutters technique is a means of intensive mixing in a forced-action mixer as evidenced by the instant specification at page 10 (as discussed in more detail above). Therefore, James et al. teach the exact same ingredients and mixing technique as required by the instant product-by-process claims. One of ordinary skill in the art would need merely to adjust the speed of the mill or cutter and the amount of flutamide fed into the machine and/or the grinding period (col. 2, lines 39-42) in order to arrive at the instantly claimed particle sizes and surface areas. Furthermore, because it is well known in the pharmaceutical art that milling/mixing is highly energy intensive and therefore costly, and that bioavailability is known to be critically dependent upon both the particle size distribution and the surface area of the resultant particles, one would be particularly motivated to experiment with these features in order to arrive at a set of flutamide particles with optimal bioavailability achieved with optimal efficiency. Further motivation for milling/mixing less and thus arriving at larger particle sizes (i.e. X_{50} greater than 26 microns, X_{90} greater than 130 microns, and a surface area greater than $0.35\text{ m}^2/\text{cm}^3$) stems from the fact that it is well

known in the flutamide formulating art that excess milling/mixing can lead to heat degradation of the product. See col. 2, lines 33-34. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

It is important to note that the phrases "unmilled" with respect to flutamide and "wherein the flutamide has been subjected to intensive mixing in a forced-action mixture [mixer] with the at least one surface-active substance" of claim 37 and "wherein the formulation is mixed in a forced-action mixer for 1 to 180 minutes" in claim 61, and "wherein the formulation is mixed in a forced-action mixture [mixer] for 3 to 60 minutes" of claim 62 are recitations of product-by-process limitations. Since claim 37 is a product-by-process claim, and all pending claims depend from claim 37, therefore, all pending claims are product-by-process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). For more information regarding product-by-process claims, please refer to MPEP 2113. Because James et al. teaches compositions having the exact same ingredients as required by the instant claims, the exact same means of mixing as recited in the instant product-by-process type claims, and further teaches that

it is well known in the flutamide formulation art that varying the mixing speed, the amount of flutamide fed into the mixer and the mixing period all influence the resulting size and surface area of the resultant flutamide particles, the limitations of these product-by-process claims is met. It would be obvious to one of ordinary skill in the art to adjust the mixing time. One would be motivated to do so in order to affect the resultant particle size. As discussed above, this particle size has been made obvious over the teachings of James et al.

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. (US 6228401) in further view of Neri et al. (US 3995060), both as per Applicant's IDS.

The teachings of James et al. are set forth above. James fails to explicitly teach that the flutamide has been subjected to recrystallization as necessitated by claim 41. Neri '060 teaches pharmaceutical formulations comprising flutamide (4-nitro-3-trifluoromethylisobutyranilide), which is necessarily either crystalline and/or amorphous, sodium lauryl sulfate (a surface-active substance) which are mixed in a bowl (column 17, lines 14-16). The mixture is not milled until subsequent steps (see column 17, lines 17-20). Furthermore, step 3 (lines 21-23) admits that the first milling contains unmilled fractions of flutamide and sodium lauryl sulfate. Neri teaches that recrystallization is a common and effective means of purifying flutamide (col. 2, line 37).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention based on the combined teachings of James and Neri to arrive at the

instant formulation comprising recrystallized flutamide with a reasonable expectation for success. One would have been motivated to do so because Neri teaches that recrystallization is a common means of purifying flutamide. Since the desired composition is for pharmaceutical use, one would be particularly motivated to have a pure substance. The more pure the drug, in this case flutamide, the fewer chances for undesired side-effects.

Applicant's data in the specification has been considered. The pharmaceutical formulations shown in working examples 1 through 6 all consist of ingredients identical to those shown in the working examples of James et al., namely flutamide, lactose, sodium lauryl sulfate (a.k.a. sodium dodecylsulfate), microcrystalline cellulose, corn (maize) starch, silica and magnesium stearate. Example 1 contains crystalline, unmilled flutamide and was intensively mixed for 3 minutes in a forced-action mixer. As discussed in the above rejection, James teaches that forced-action mixers (i.e. rotary cutters) are a means of mixing the flutamide mixture. Subsequent examples use either crystalline unmilled flutamide, micronized flutamide. Different mixing mechanisms are used, including a forced-action mixer, a free fall mixer etc. As taught in James, several different known milling and mixing all techniques give rise to different particle sizes, size distribution and surface areas, and these particle qualities can be easily manipulated by adjusting the speed of the mill, the amount of flutamide fed into the mill and the grinding period. Applicant's specification provides no examples or data demonstrating that the size of the flutamide of the instantly claimed formulations is somehow unexpectedly

different or beneficial over that which would be expected from the teachings of the prior art.

Response to Arguments

Applicant's arguments filed 10/29/2009 regarding the rejection of claims over James et al. alone and in view of Neri et al. have been fully considered, but are not persuasive.

Applicant argues that James et al. teaches away from the present invention and therefor cannot render the claimed invention obvious. In support of this argument, applicant argues that because James teaches that particle size is critical and teaches that you should never go above $X_{50} = 26.0 \mu\text{m}$ and preferably teaches particle sizes in the range of 5.0 to 20.0 μm (col. 2, lines 23-25), James clearly teaches away. Applicant also argues that due to the preferred particle sizes and surfaces areas taught by Jones, that a skilled artisan would have had no reason to conclude that the instantly claimed flutamide particles possess adequate bioavailability. Applicant also points to col. 2, lines 30-45 and claims that this section does not provide support for the Examiner's analysis that excess milling/mixing can lead to heat degradation of the product. These arguments are not persuasive.

As addressed in the above rejection, James teaches X_{50} and X_{90} values that overlap with and which are very close to those values claimed and specific surface areas that are very close to those ranges claimed by applicant. Furthermore, James teaches that flutamide is known to exist in particle sizes up to 240 microns and also teaches that it is known in the art to achieve similar particle sizes, as measured by X_{50}

and X_{90} values, and different specific surface areas by using rotary cutters or other milling techniques. Furthermore, because it is well known in the pharmaceutical art that milling/mixing is highly energy intensive and therefore costly, and that bioavailability is known to be critically dependent upon both the particle size distribution and the surface area of the resultant particles, one would be particularly motivated to experiment with these features in order to arrive at a set of flutamide particles with optimal bioavailability achieved with optimal efficiency. Attention is directed to MPEP 2144.05 which teaches that "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Here, both particle size distribution and surface area are recognized by Jones et al. to be result effective variables, as they both influence the resulting bioavailability and achieving these different particle sizes and surface areas is known to be energy intensive. It is further noted that applicant's claims do not currently recite any bioavailability requirements.

Further motivation for milling/mixing less and thus arriving at larger particle sizes (i.e. X_{50} greater than 26 microns, X_{90} greater than 130 microns, and a surface area greater than $0.35 \text{ m}^2/\text{cm}^3$) stems from the fact that it is well known in the flutamide formulating art that excess milling/mixing can lead to heat degradation of the product. This fact can not only be gleaned from col. 2, lines 30-45 of Jones et al., but it is well known in the art that mixing causes friction and friction leads to heat and heat leads to the degradation of pharmaceutical products. After all, why would Jones et al. mention

chemical and/or head degradation of flutamide in the context of milling? It is noted that applicant has not provided data demonstrating the unexpected properties of a larger particle size.

In summary, James et al. teaches compositions having the exact same ingredients as required by the instant claims, the exact same means of mixing as recited in the instant product-by-process type claims, that bioavailability depends on the surface area and size distribution of the flutamide particles, and further teaches that it is well known in the flutamide formulation art that varying the mixing speed, the amount of flutamide fed into the mixer and the mixing period all influence the resulting size and surface area of the resultant flutamide particles. Accordingly, as discussed in greater detail above, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at the claimed invention with a reasonable expectation for success. The claims are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al. alone and in view of Neri et al. Although the invention is not identically disclosed or described as set forth in 35 U.S.C. 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a designer having ordinary skill in the art to which said subject matter pertains, the invention is not patentable. Applicant has not provided evidence proving that the claimed particle sizes and surface areas are somehow unexpected over the teachings of James et al.

Conclusion

Claims 37-41, 46, and 49-62 are rejected. No claim is allowed.

No new ground(s) of rejection were presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kortney Klinkel, whose telephone number is (571)270-5239. The examiner can normally be reached on Monday-Friday 8am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Art Unit: 1611

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KLK

/Ashwin Mehta/
Primary Examiner, Technology Center 1600